• **Apolipoprotein A-I (Apo-AI)** is the major protein constituent of the HDL particles.

• **Apo-AI fusion proteins** have an optimized pharmacokinetic/pharmacodynamic profile as they show the following properties:
  - Apo-AI increases the plasmatic **half-life** and the **liver** retention of the fused proteins.
  - **Blood-brain barrier active transport**, mediated by a saturable transporter that limits the amount of the fusion protein in the central nervous system.
  - **Modulation of activity**: Apo-AI activates MAPKs through ABCA1 and SR-BI and, therefore, modulates the therapeutic effect of fused proteins.

• **Sushi-IL-15-Apo** is a new **proprietary triple fusion protein** developed combining apolipoprotein A-I, IL-15 and IL-15Rα’s sushi, with:
  - Superior antitumor effect than IL-15 as a single agent.
  - Higher capacity than hIL15 to enhance antibody dependent cell cytotoxicity (ADCC) when combined with monoclonal antibodies.
  - Increased stability in circulation.
  - Facilitated trans-presentation.

• **Primary Indication**: adjuvant of tumor specific antigen antibodies in lymphoma, breast cancer and colorectal cancer treatment.

### Medical need
Enhancement of the immune response against the tumors with emphasis in **synergistic approaches** with the current standard of care.

### Proof of Concept
- Immunotherapeutic effects against metastatic disease in *in vivo* tumor models, (B16OVA lung metastasis of melanoma & MC38 colon cancer liver metastasis).
- *In vitro* assays testing the ADCC capacity of Sushi-IL15-Apo in combination with cetuximab against colorectal cancer-derived cell lines.

### Safety
- Toxicity is an on-target side effect; a therapeutic window has been found.
- Repeated doses are feasible without desensitization or cumulative toxicity.

### Product Profile
- A plasmid encoding a triple fusion protein combining apolipoprotein A-I, IL-15 and the Sushi domain.
- Apo A-I acts as a natural vehicle that facilitates the IL-15/IL-15Ra sushi domain anchorage for trans-presentation of the cytokine.
- pSushi-IL-15-Apo is highly active and plasmid doses within the therapeutic range have been identified.
- These plasmid doses were tolerated and promoted the proliferation and accumulation of NK and memory CD8+ T cell in the spleen and in the liver (Fig. 1 and Fig. 2).
- In a classical chromium release assays it has been shown that human Sushi-IL15-Apo protein increases ADCC capacity of cetuximab against a tumoral cell line (Fig. 3).

![Fig.1. pSushi-IL-15-Apo gene transfer to the liver ameliorates melanoma lung metastasis of B16OVA.](image1)

![Fig.2. pSushi-IL-15-Apo hydrodynamic gene transfer is active against liver metastases of MC38 colon carcinoma.](image2)

![Fig.3. Human Sushi-IL-15-Apo increases ADCC capacity of cetuximab in chromium51 release assays against HT-29 colon carcinoma cells.](image3)

### Apo Platform:
- InterApo: ApoA-I fused to IFNα.
- Apo-Linker-144: Apo-AI fused to P144, an inhibitor peptide of TGFβ.
- Apo-CT1: Apo-AI fused to cardiotrophin 1.
- Other fusion proteins are under development.

### Intellectual Property

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